REMARKS

Status of the Claims

Claims 1-13, 21-26, and 28-30 are currently pending and under examination. Applicants respectfully request reconsideration of the application in view of the following remarks.

Enablement Rejections Under 35 U.S.C. § 112, first paragraph

The rejection of Claims 1-13, 21-26, and 28-30 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement, was maintained. Applicants respectfully traverse the rejections.

In particular, the Office Action repeated the prior §112 rejections, alleging that: A) the specification is not enabling for apelin antisense therapy in view of prior art teachings suggesting unpredictability of the antisense therapy; B) the specification and prior art is not enabling for inhibiting angiogenesis with any apelin antibody in any subject much less a human; and C) the specification and prior art is not enabling for inhibiting apelin activity in a human with an antibody against zebrafish apelin (SEQ ID NO:5).

In response to Applicants' arguments submitted on 06/10/08 for rejections based on reasons A-C as mentioned above, the Office Action further alleged that for the rejection based on reason A, the prediction of drug effects in any animal model much less a human based solely on a single *in vitro* frog embryo model experiments is not reliable and further evaluation in animal angiogenic tumor systems is essential because, in view of the unpredictable correlation between *in vitro* and *in vivo* animal studies much less a human study, one skilled in the art would reasonably conclude that evidence obtained from the *in vitro* frog embryo model would not even necessarily correlate with results expected in a relevant angiogenic tumor animal model much less in a human.

For the rejection based on reason B, the Office Action further alleged that because the claims are directed to antibodies having the ability to bind to one or more of the peptide species as set forth in the Markush group, Applicants are required to show the cross-reactivity for the antibodies amongst the different peptides. Furthermore, the Office Action alleged that the Applicants are not exonerated from having to meet the burden of enablement especially for

antibody immunotherapeutics, where a limited number of experiments do not provide a sufficient correlation or nexus for the use of the antibody to treat a cancer *in vivo* much less in a human, and a relevant model would be an animal model at least bearing some resemblance to tumor angiogenesis.

For the rejection based on reason C, the Office Action stated that Applicants allege that SEQ ID NO:5, which is a peptide from zebra fish and differs by only one amino acid from the human-derived apelin peptide of SEQ ID NO:4, should generate similar antibodies relative to the antibodies of SEQ ID NO:4. However, the Office Action further alleged that Applicants have not shown that the zebra fish peptide is relevant to any tumor angiogenesis model, that the peptide would generate a therapeutic antibody and that the same antibody would possess tumor angiogenesis-inhibitory activity *in vivo*.

Applicants respectfully disagree with all the allegations summarized above, and respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to make and use the invention as recited in the currently pending claims.

The discovery for which Applicants are entitled a patent is that angiogenesis can be inhibited by inhibition of apelin activity. The powerful and simple principal has been demonstrated by Applicants with two exemplary classes of inhibitors, antisense and antibodies, in *in vitro* and *in vivo* models. It is not necessary for Applicants to demonstrate every embodiment encompassed by the claims, when the results demonstrated are reasonably predictive of the likely success of those other embodiments, and they can be routinely screened by others skilled in the art.

The specification provides sufficient working examples showing that an inhibitor of apelin activity, *e.g.*, an apelin antisense DNA, does inhibit vascular growth or angiogenesis in an art-accepted animal model (*e.g.*, Example 5). The Declaration of Dr. Krieg, dated September 18, 2007, also demonstrates that "an apelin antisense oligonucleotide does in fact inhibit angiogenesis" in an art-accepted model. Although the art recognized unpredictability in the use of antisense molecules, Applicants respectfully submit that given this demonstration, it would be reasonably expected that other antisense apelin inhibitors could routinely be made and tested and, therefore, enabled such that one skilled in the art could practice the claimed invention.

Moreover, Applicants respectfully point out that the angiogenesis model system of *Xenopus* embryos used in the instant specification is an art-accepted ***in vivo***, not an *in vitro*, animal model to study angiogenesis. Example 5 shows that an apelin antisense oligonucleotide inhibits angiogenesis in this angiogenesis model system of *Xenopus* embryos. *See* instant specification, pages 33-34, paragraphs [0106]-[0112]. Apelin antisense morpholino oligonucleotides (or mismatch controls) were injected into one cell of a 2 cell frog embryo along with Texas Red as a lineage tracer. Embryos were grown to stage 35 and then assayed by *in situ* hybridization using the vascular marker erg. The antisense oligonucleotides resulted in a 67% inhibition of angiogenic growth of embryonic blood vessels, including inhibition of the development of the intersomitic vessels (*See* Figure 9 of instant specification). Similar results were obtained with antisense oligonucleotides to the APJ receptor; however, mismatch control oligonucleotides did not detectably affect the vascular growth of the embryos. These results show that the apelin antisense molecules specifically inhibit angiogenesis in an art-accepted ***in vivo*** model system for angiogenesis.

Thus, in view of the *in vivo* angiogenesis inhibition in the model system of *Xenopus* embryos demonstrated in the instant specification, and the rejection based on this misunderstanding is moot.

With respect to the Office Action's requirement to show the cross-reactivity for the antibodies amongst the different peptides to demonstrate that the antibodies could bind to any one or more of the peptides of SEQ ID NO: 1-5, Applicants respectfully submit that one skilled in the art would appreciate that the generation of antibodies is routine in the art as are methods of determining the specificity, effectiveness, and cross-reactivity of those antibodies. Determining those additional antibodies bind to and inhibit the activity of apelin as expected is routine. In fact, the specification, together with the relevant skill in the art, enables one to practice the claimed invention, because the generation and screening of antibodies to one or more peptides is routine in the art.

Dr. Krieg in his Declaration demonstrates that several anti-apelin antibodies can specifically bind to apelin, and thereby affect the activity of apelin in an art-accepted angiogenesis model. Applicants respectfully submit that this evidences the enablement of the

claimed invention, and it is not required that Applicants specifically demonstrate that each embodiment of apelin antibodies that bind to the peptides of SEQ ID NOs:1-5 can generate anti-angiogenesis responses in any sample from any subject, in any species and to what degree. Therefore, Applicants are not required to show the cross-reactivity for the antibodies amongst the different peptides in order to meet the enablement requirement for the claimed invention.

Moreover, Applicants respectfully submit that the specification and Dr. Krieg's Declaration provide sufficient evidence of *in vivo* animal models for the claimed method of inhibiting angiogenesis. Both model system of *Xenopus* embryos and CAM model are art-accepted angiogenesis models. The purpose of a model system is to allow one to determine the effectiveness of a treatment in that model to specifically avoid having to perform those tests in any sample from any subject, in any species and to what degree. Clearly, the patentability standard for demonstrating a reasonable expectation of success without undue experimentation for enablement, and the standard for initiating human clinical trials are intentionally very distinct. Applicants respectfully submit that the Office Action appears to reject the validity of the art-accepted models used to demonstrate the claimed invention, but does not present any objective evidence why these models are not acceptable, and the Office Action errs to limit the relevant animal model to tumor angiogenesis model since the discovery is not limited to inhibiting angiogenesis for only one purpose.

Moreover, the Office Action alleged that Applicants have not shown that the zebra fish peptide (SEQ ID NO:5) is relevant to any tumor angiogenesis model, and that a peptide would generate a therapeutic antibody and that the same antibody would possess tumor angiogenesis-inhibitory activity *in vivo*. Applicants respectfully submit that similar to SEQ ID NO:4, the specification clearly states that SEQ ID NO:5 is one of the "apelin polypeptides" that refer to a polypeptide that comprises the C-terminal 13 amino acids of apelin ("apelin-13"). As previously discussed, SEQ ID NO:5 and SEQ ID NO:4 differs by only one amino acid. Since Example 3 of the specification provides an example demonstrating the angiogenic effect of SEQ ID NO:4, the specification does not need to provide the angiogenic effect for all apelin-13 peptides, including SEQ ID NO:5. Therefore, Applicants do not need to show that all the apelin-13 peptides,

including SEQ ID NO:5, are relevant to an angiogenesis model to meet the enablement requirement.

Therefore, for the foregoing reasons, Applicants respectfully submit that the specification is sufficient to enable one of ordinary skill in the art to make and use the invention as recited in the currently pending claims. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

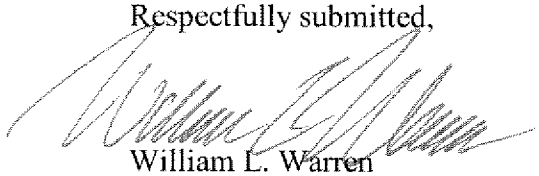
Conclusion

Applicants believe that the present application, as amended, is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The foregoing is submitted as a full and complete response to the Office Action mailed September 5, 2008.

A petition for a five-month extension of time and a request for continuing examination are enclosed, along with the appropriate fees therefor. It is not believed that any additional extensions of time or fees for net addition of claims are required. However, please charge any additional fees that may be due, or credit any overpayment, to Deposit Account 19-5029 (Ref. No.: 20825-0004).

In addition, if there are any issues that can be resolved by a telephone conference or an Examiner's amendment, the Examiner is invited and encouraged to call the undersigned attorney at (404) 853-8000.

Respectfully submitted,



William L. Warren
Reg. No. 36,714

Date: October 5, 2009
SUTHERLAND ASBILL & BRENNAN LLP
999 Peachtree Street, NE
Atlanta, Georgia 30309-3996
(404) 853-8000
Sutherland Docket: 20825-0004